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09/672,126	09/27/2000	Gunther Hartmann	C1039/7044 (AWS)	6887

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EXAMINER	
NGUYEN, QUANG	
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1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/672,126	Applicant(s) HARTMANN ET AL.	
	Examiner Quang Nguyen	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,47,65,82,103,122,143,159,176,199 and 201-203* is/are pending in the application.

4a) Of the above claim(s) *47,122,143,159,199 and 201* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,65,82,103,176,202 and 203* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-24, 47, 65, 82, 103, 122, 143, 159, 176, 199 and 201-203 are pending in the present application.

Applicants' election with traverse the invention of Group I (claims 1-24, 65, 82, 103, 176, 199 and 202-203) in Paper No. 9 dated March 25, 2002 is acknowledged. Additionally, Applicants elected with traverse the following SEQ ID NOs: 7, 9, 11, 13, 24, 25, 30, 33, 36 and 37.

With respect to the traverse election of Group I, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). With respect to the traverse election of SEQ ID NOs as distinct nucleic acid sequences, Applicants argue that the described oligonucleotides in the claims share a common structural motif, similar to a chemical structure, and therefore the class of oligonucleotides should be treated as species/genus rather than as completely separate and distinct nucleic acid sequences. Applicants' argument is respectfully found to be unpersuasive because Applicants fail to point out which common structural motifs that SEQ ID NOs: 2-37 share among each other. It is noted that unlike the elected SEQ ID NOs 7, 9, 13, 24-25, 30, 33, 36-37 having CG dinucleotides within the palindromic sequences, other nucleic acid sequences such as SEQ ID NOs: 2-6, 8, 14, for examples, do not contain CG dinucleotides within panlindromic sequences. Moreover, unlike the elected SEQ ID NOs, SEQ ID NOs: 2-4 also contain T-enriched sequences. Furthermore, the instant specification specifically teaches that ODN 2198 containing a

CG dinucleotide, poly G ends but no palindrome is essentially inactive in inducing IFN-α in PBMC in comparison with ODN 1585 (SEQ ID NO:1) or ODN 2216 (SEQ ID NO:7) (see example 5). Therefore, because the claims encompass nucleic acid sequences that do not contain substantial common core structures that yield the same functions (e.g., inducing IFN-α in PBMC, for example), and because of the limited resources from the US PTO to conduct the computer search of the claimed SEQ ID NOs, an undue burden would be needed to search and examine all of the claimed SEQ ID NOs, restriction for examination purpose as indicated is proper. This is made FINAL.

Claims 47, 122, 143, 159 and 201 are withdrawn from further consideration because they are drawn to non-elected inventions.

Accordingly, claims 1-24, 65, 82, 103, 176, 199 and 202-203 are examined on the merits herein.

Sequence compliance

The disclosure is objected to because of the following informalities: The specification contains sequence listings. The sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 (See page 68, lines 25 and 26 of the instant application for examples). It should be noted that for any peptide sequence longer than 3 amino acid residues, a SEQ ID NO must be assigned to each peptide sequence. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1,

1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82(June 23, 1998).

Appropriate correction is required.

Claim Objections

Claim 176 is objected to because it contains the abbreviations "IFN" and "IPCs" that should be written out at the first occurrence of the terms. Appropriate correction is required.

Claims 19 and 202-203 are objected because they contain non-elected SEQ ID NOs.

Written Description

Claims 1-11, 17-18, 20-24, 65, 82, 103, 176 and 199 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to methods utilizing an effective amount of an isolated immunostimulatory nucleic acid to improve a method calling for the administration of IFN-α or for supplementing IFN-α treatment of a subject or for increasing efficacy of IFN-α treatment of a subject or for decreasing a dose of IFN-α effective for treating a subject or for stimulating production of a plurality of type I IFN subtypes in natural interferon producing cells (IPCs) as well as for inhibiting IL-12 production in IL-12 producing cells. Apart from disclosing that the immunostimulatory nucleic acid molecule having at least a T-rich motif, a poly-G rich sequence or a CpG motif, the instant specification fails to teach a representative number of species for a broad genus of an isolated immunostimulatory nucleic acid molecule which is capable of inducing contacted cells of the immune system to proliferate and/or to become activated to improve any method which calls for the administration of IFN-α or for stimulating production of a plurality of type I IFN subtypes in IPCs or for inhibiting IL-12 production in IL-12 producing cells. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48

USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure or critical elements of any immunostimulatory nucleic acid molecules other than those possessing at least one of a T-rich motif, a poly-G rich sequence or a CpG motif. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 17-18, 20-24, 65, 82, 103, 176, 199 and 202-203 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) An improved *in vitro* method calling for the administration of IFN-α, the improvement comprising administering an effective amount of an isolated

immunostimulatory nucleic acid molecule, wherein said immunostimulatory nucleic acid molecule comprises (i) poly(G) sequences at both ends, (ii) a central panlindromic sequence, and (iii) unmethylated CG dinucleotides within the palindrome, and said isolated immunostimulatory nucleic acid molecule is at least 8 nucleotides in length;

(2) An *in vitro* method of stimulating production of a plurality of type I IFN subtypes, comprising administering to natural interferon producing cells (IPCs) with an amount of immunostimulatory nucleic acid effective to induce secretion of at least two type I interferons, wherein said immunostimulatory nucleic acid comprises (i) poly(G) sequences at both ends, (ii) a central panlindromic sequence, and (iii) unmethylated CG dinucleotides within the palindrome, and said isolated immunostimulatory nucleic acid molecule is at least 8 nucleotides in length;

(3) An *in vitro* method of inhibiting IL-12 production, said method comprises administering to IL-12 producing cells, in the presence of interferon-producing cells under conditions in which the IL-12-producing cells normally produce IL-12, with an immunostimulatory nucleic acid in an amount effective for inducing secretion of type I interferon wherein said immunostimulatory nucleic acid comprises (i) poly(G) sequences at both ends, (ii) a central panlindromic sequence, and (iii) unmethylated CG dinucleotides within the palindrome, and said isolated immunostimulatory nucleic acid molecule is at least 8 nucleotides in length;

does not reasonably provide enablement for the use of any immunostimulatory nucleic acid and the *in vivo* embodiments of the claims. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1-24 are drawn to a method which calls for administration of IFN-α, the improvement comprising co-administering an effective amount of an isolated immunostimulatory nucleic acid.

Claim 24 is directed to a method of supplementing IFN-α treatment of a subject comprising administering to the subject in need of IFN-α treatment an effective amount of IFN-α and an isolated immunostimulatory nucleic acid. Claim 65 is drawn to a method of increasing efficacy of IFN-α treatment of a subject comprising administering to a subject in need of treatment with IFN-α a pharmaceutical composition comprising IFN-α, and coadministration to the subject in need of such treatment a pharmaceutical composition comprising an immunostimulatory nucleic acid in an amount which, together with the administered IFN-α, is an effective IFN-α treatment, wherein the efficacy of the IFN-α treatment is greater than the efficacy of administering the same amount of IFN-α in the absence of coadministering the immunostimulatory nucleic acid.

Claim 82 is drawn to a method of decreasing a dose of IFN-α effective for treating a subject, comprising: administering to a subject in need of treatment with treatment with IFN-α a pharmaceutical composition comprising IFN-α, and coadministration to the subject in need of such treatment a pharmaceutical composition comprising an immunostimulatory nucleic acid in an amount which, together with the administered IFN-α, is an effective IFN-α treatment, wherein the amount of administered IFN-α is less than an amount of IFN-α required in the absence of coadministering the immunostimulatory nucleic acid.

Claim 103 is directed to a method of preventing an IFN-α treatment related-side effect in a subject receiving or in need of treatment with IFN-α, comprising administering to a subject in need of treatment with IFN-α a pharmaceutical composition comprising IFN-α, and coadministering to the subject in need of such treatment a pharmaceutical composition comprising an immunostimulatory nucleic acid in an amount which, together with the administered IFN-α, is an effective IFN-α treatment, and wherein an IFN-α treatment-related side effect is reduced in comparision to the side effect when IFN-α is administred in the absence of coadministering the immunostimulatory nucleic acid.

Claim 176 is drawn to a method of stimulating production of a plurality of type I IFN subtypes, comprising contacting natural interferon producing cells (IPCs) with an amount of immunostimulatory nucleic acid effective to induce secretion of at least two type I interferons.

Claim 199 is drawn to a method of inhibiting IL-12 production, comprising contacting IL-12 producing cells, in the presence of interferon-producing cells under conditions in which the IL-12 producing cells normally produce IL-12, with an immunostimulatory nucleic acid in an amount effective for inducing secretion of type I interferon.

Claims 202-203 are drawn to a pharmaceutical composition comprising an isolated nucleic acid having a sequence of elected SEQ ID NOs, and a pharmaceutically acceptable carrier; the same further comprising IFN-α.

The instant specification is not enabled for the instant broadly claimed inventions for the reasons discussed below.

The instant claims encompass the utilization of any immunostimulatory nucleic acid molecule to improve any method (both *in vitro* and *in vivo*) which calls for the administration of IFN-α, which when read in light of the specification the sole purpose for an *in vivo* method is for achieving therapeutic effects for a subject having a proliferative disorder or a viral infection, for supplementing IFN-α treatment of a subject, for increasing efficacy of IFN-α treatment of a subject, for decreasing a dose of IFN-α effective for treating a subject, for preventing an IFN-α treatment-related side effect in a subject receiving or in need of treatment with IFN-α, for stimulating production of a plurality of type I IFN subtypes in natural interferon producing cells (IPCs), and for inhibiting IL-12 production in IL-12 producing cells. The present disclosure is not enabled for such a broadly claimed invention for the same reasons set forth in the lack of the Written Description section above. Apart from disclosing that the

immunostimulatory nucleic acid molecule having at least a T-rich motif, a poly-G rich sequence or a CpG motif, the instant specification fails to teach a representative number of species for a broad genus of any isolated immunostimulatory nucleic acid molecule to attain the desired results contemplated by Applicants in the methods (both *in vitro* and *in vivo*) as claimed. Therefore, given the lack of sufficient guidance provided by the present application it would have required undue experimentation for a skilled artisan to make and use the full breadth of the claims.

The claims encompass the utilization of non-CpG immunostimulatory nucleic acid molecules (e.g, poly-G nucleic acid molecule or T-rich nucleic acid molecule) to improve any method which calls for the administration of IFN-α, for supplementing IFN-α treatment of a subject, for increasing efficacy of IFN-α treatment of a subject, for decreasing a dose of IFN-α effective for treating a subject, for preventing an IFN-α treatment-related side effect in a subject receiving or in need of treatment with IFN-α, for stimulating production of a plurality of type I IFN subtypes in natural interferon producing cells (IPCs), and for inhibiting IL-12 production in IL-12 producing cells. However, there is no evidence of record indicating or suggesting that any non-CpG immunostimulatory nucleic acid molecule is capable of producing the desired results contemplated by Applicants for the methods as claimed. On the contrary, the specification specifically teaches that ODN 1585 (ggGGTCAACGTTGAggggggG, SEQ ID NO: 1, containing CG dinucleotide in a palindrome) can inhibit the production of IL-12 whereas ODN 2006 (tctcgttttgtcgttttgtcgtt, SEQ ID NO:147, containing CG dinucleotides without a palindrome) do not inhibit the production of IL-12 (see example 13). Additionally, the

specification teaches that only certain CpG oligonucleotides such as ODN 1585 (SEQ ID NO:1), ODN 2216 (ggGGGACGATCGTCgggggG, SEQ ID NO:7), all of which contain at least one CG dinucleotide in a palindromic sequence, are capable of inducing plasmacytoid dendritic cells (pDC), the **principle type I interferon producing cells** in human blood and a critical effector cell type of the immune system for antiviral and antitumor responses (Siegal et al., Science 284:1835-1837, 1999, IDS), to produce IFN-α, and not other CpG containing oligonucleotides such as ODN 2006 (see examples 5-6), let alone for any immunostimulatory nucleic acid molecule. It is further noted that control oligonucleotides for ODN 2216 such as ODN 2197 (7-deaza-guanosine substations in poly G ends, unable to form G tetrads) and ODN 2198 (CG and poly G ends but no palindrome) do not induce any significant amount of IFN-α in PBMC; nor do poly (I:C) molecule (see example 5). Therefore with the lack sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make the full breadth of the claimed methods, particularly Applicants have also noted from *in vitro* studies that ODN induced IFN-α in human pDC enriched PBMCs to varying degrees, and that the induction of IFN-α in human PBMCs is variable depending on the donor source (see examples 16 and 17). As such, it certain would have required undue experimentation for a skilled artisan to attain the desired results (e.g., supplementing IFN-α treatment in a subject, increasing efficacy of IFN-α treatment in a subject, decreasing a dose of IFN-α effective for treating a subject or preventing an IFN-α treatment-related side effect in a subject) in the methods as claimed, particularly in the absence of any relevant *in vivo* example (part of guidance). Furthermore, the

physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The instant claims encompass the utilization of an immunostimulatory nucleic acid molecule of any length to obtain the desired results contemplated in the claimed methods. It is unclear whether an immunostimulatory sequence as short as 2 or 4 or 6 base pairs would also capable of yielding the desired results. Morevover, it is well established in the prior art that an immunostimulatory DNA sequence must contain at least unmethylated CpG dinucleotides in a consensus motif of 5'-purine-purine-CpG-pyrimidine-pyrimidine-3' (Krieg et al., U.S. Patent No. 6,194,388; IDS, U.S. Patent No. 6,239,116; IDS; U.S. Patent No. 6,214,806; IDS), and for an efficient uptake by cells, oligonucleotides in the range of 8 to 40 base pairs in size would also be needed. As such, in the absence of evidence to the contrary it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods as claimed, using any isolated immunostimulatory nucleic acid molecule of less than 8 nucleotides in size.

With respect to claims drawn to *in vivo* methods, the instant specification does not provide sufficient guidance for a skilled artisan on how to target any immunostimulatory nucleic acid molecule to the desired target cells, e.g. plasmacytoid

dendritic cells (pDC) or natural interferon-producing cells (IPCs), the **principle type I interferon producing cells** in human blood, and IL-12 producing cells to attain the desired results contemplated by Applicants (e.g., increase efficacy of IFN-α treatment of a subject including improvements such as decreasing an effective utilized dose of IFN-α, preventing an IFN-α treatment-related side effect; stimulating production of a plurality of type I IFN subtypes as well as inhibiting IL-12 production). At the effective filing date of the present application, *in vivo* vector targeting continues to be unpredictable and highly inefficient. This is supported by numerous teachings in the art. For examples, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art that show promises, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy and the problems that are associated with each and clearly indicated that the resolution to *in vivo* vector targeting had not

been achieved in the art (see the entire article). The specification fails to provide sufficient guidance for a skilled artisan how to overcome the unpredictability of *in vivo* vector targeting, such that an efficient transfer of any immunostimulatory nucleic acid molecule to the aforementioned specific cell populations could be attained to effect the desired results contemplated by Applicants, particular by any route of administration as encompassed by the scope of the claims. It is further noted that as written the claims do not even require that the administered immunostimulatory nucleic acid molecule contains any modified nuclease-resistant backbone to effect the desired results *in vivo*. However, it is well known in the art that naked nucleic acid molecule or oligonucleotides are susceptible to nuclease degradation, particularly via an intravenous delivery. Then, how can an effective amount of an immunostimulatory nucleic acid molecule be delivered to the desired cell populations to obtain the desired results? Furthermore, at the effective filing date of the present application, it should be noted that the attainment of therapeutic effects via gene therapy (for this instance delivery of an immunostimulatory nucleic acid molecule to certain cell populations) in general was highly unpredictable. Therefore, with the lack of sufficient guidance provided by the instant specification, and in the absence of any relevant *in vivo* example (part of guidance), it would have required undue experimentation for one skilled in the art to make and use the methods as claimed.

With respect to claims 202-203 drawn to a pharmaceutical composition, the instant specification fails to provide sufficient guidance for a skilled artisan on how to use the claimed composition to obtain any therapeutic effects *in vivo*, for the reasons

already discussed in the immediate preceding paragraph. As such, it would have required undue experimentation for a skilled artisan to use the pharmaceutical composition to attain therapeutic effects contemplated by Applicants.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art and gene therapy, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-7, 20-23 and 103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-7 and 20-23 recites the limitation "the subject" in the claims. There is insufficient antecedent basis for this limitation in the claim. This is because there is no recitation of any subject in claim 1, from which these claims are dependent upon.

In claim 103, there is no correlation between the preamble of the claim reciting "**preventing** an IFN-α treatment-related side effect" with the phrase "treatment-related side effect **is reduced"** as the result of the claimed method. Do Applicants intend to claim a method of preventing or reducing an IFN-α treatment-related side effect in a subject? The metes and bounds of the claim are not clearly determined.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER